REMARKS

At the outset, Applicant wishes to thank the Examiner for the courtesy of a telephonic interview on June 12, 2007. During the interview, novel and non-obvious aspects of the invention were discussed and amendments to the claims were proposed to clarify the claimed subject matter in keeping with these aspects of the invention. References cited in the Office Action dated February 27, 2007 were also reviewed in relation to the claims. Arguments further supportive of the novelty of the claimed subject matter were also discussed. The Examiner's suggestions and guidance in this regard are greatly appreciated.

Claims 1-42 are pending. Claims 4-8, 12, 13, and 16-38 are withdrawn from consideration. Claims 1 and 39-42 are amended herein. Claim 3 is canceled herein without prejudice. Claims 2 and 9-11 were previously canceled. Accordingly, claims 1 and 39-42, as amended, and dependent claims therefrom, are presently under consideration.

Support for amendment to the claims is found throughout the specification and in the original claims. Specifically, support for amendment to claims 1 and 39-42 is found in original claims 1 and 3. No issue of new matter is introduced by these amendments.

Rejection Under 35 U.S.C. § 102

Claims 1, 3, 14, and 15 stand rejected and new claims 39-42 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Platt et al. [1998; IDS AF; United States Patent Number (USPN) 5,786,368]. The claims are amended herein to be directed to a combination of N-butyldeoxynojirimycin (NB-DNJ) and glucocerebrosidase. Applicant asserts that Platt et al. (1998) do not teach the recited combination. In view of the clarifying amendments to the claims and Applicant's arguments presented herein, the rejection as it applied to claims 1, 3, 14, 15, and 39-42 is respectfully traversed.

Supportive of Applicant's assertion, Platt et al. (1998; IDS AF) state that NB-DNJ is known to be an inhibitor of lysosomal glucocerebrosidase, an enzyme required for the cleavage of Glc-Cer to glucose and ceramide. See column 10, lines 46-50. Moreover, Platt et al. teach that the N-butyl derivative of DNJ acts as an inhibitor of glucocerebrosidase in a cellular environment. See column 10, lines 50-56. Platt et al. also present direct experimental evidence demonstrating that NB-DNJ exhibits moderate inhibition of glucocerebrosidase. See Column 10, lines 56-67 and Table 5. In view of the above, these

authors clearly did not appreciate that a combination of NB-DNJ and enzyme augmentation would be of any utility. Indeed, the disclosure of Platt et al. would teach a skilled artisan that such a combination would be contraindicated in a method directed to reducing accumulation of glucosylceramide-containing glycolipids in a patient afflicted with a glycolipid storage-related disorder. Thus, this reference fails to anticipate the methods of the present invention.

Claims 1, 3, 14, and 15 stand rejected and new claims 39-42 are under 35 U.S.C. §102(b) as allegedly anticipated by Aerts et al. (1998; IDS AH). As indicated above, the claims are amended herein to be directed to a combination of N-butyldeoxynojirimycin (NB-DNJ) and glucocerebrosidase. Applicant asserts that Aerts et al. (1998) do not particularly or explicitly teach the recited combination. In view of the clarifying amendments to the claims, Dr. Olivier H. Morand's Declaration, and Applicant's arguments presented herein, the rejection as it applied to claims 1, 3, 14, 15, and 39-42 is respectfully traversed.

As indicated throughout, the Aerts et al. application is directed to the generation of novel deoxynojirimycin derivatives containing a large hydrophobic moiety linked through a spacer and their use as inhibitors of non-lysosomal glucosylceramidase and potential use in the treatment of diseases involving a ceramide-mediated signaling process, such as Gaucher disease. See, for example, the Abstract. Aerts et al. repeatedly emphasize that therapeutic approaches that rely on "substrate deprivation therapy" suffer from the fact that such approaches a priori inhibit the synthesis of more complex glycosphingolipids, as well as glucosylceramide synthesis. Aerts et al. further state that the presently available inhibitors of glucosylceramide synthase are known to exert a spectrum of significant biological effects that impede their applicability as therapeutic agents. In this context, NB-DNJ is known to inhibit lysosomal glucocerebrosidase and α-glucosidase I, an endoplasmic reticulum (ER) enzyme that plays a critical role in trimming of N-linked glycans in newly formed glycoproteins and accordingly, is important for maintaining quality control of protein folding. Yet another cited disadvantage of the presently available glucosylceramide synthase inhibitors, including NB-DNJ, is that these inhibitors induce the synthesis of glucosylceramide synthase, which in turn, increases the load on glucosylceramide. See page 9, lines 1-21. In light of these statements and others presented throughout the specification, it is evident that Aerts et al. view the inhibitors available at the time, including NB-DNJ, as exhibiting a lack of specificity of action that renders these compounds untenable for therapeutic use. The application is,

indeed, directed to addressing the problem of the dearth of glucosylceramide synthase inhibitors that are sufficiently specific to commend their use as potential therapeutics. Aerts et al. propose to solve this problem by generating novel deoxynojirimycin derivatives containing a large hydrophobic moiety linked through a spacer. This is explicitly stated at page 15, lines 18-21. The intended properties of the desired potent and specific inhibitor of glucosylceramidase are set forth in the Aerts et al. application at page 15, lines 22-36. It is noteworthy that NB-DNJ has a short n-butyl chain, rather than a large hydrophobic group attached to a spacer. NB-DNJ does not, therefore, possess all of the desired features that are taught by Aerts et al. for a novel potent and specific inhibitor of non-lysosomal glucosylceramidase. In keeping with the teachings of Aerts et al., NB-DNJ is not a potent and specific non-lysosomal glucosylceramidase inhibitor, but rather a non-specific inhibitor at best.

Moreover, the assessment of NB-DNJ as a potential therapeutic for use in combination with enzyme replacement, as set forth by Aerts et al., is representative of expert opinion in the field. Indeed, the recognized defects of NB-DNJ that were thought to render it unsuitable for use as a therapeutic in combination with enzyme replacement were well known at the time of filing of the Aerts et al. application. More to the point and as described previously, there was a significant technical prejudice against combining NB-DNJ and enzyme augmentation for the treatment of glycolipid storage disorders at the priority date of the present application because NB-DNJ is a known inhibitor of glucocerebrosidase (IC_{50} = 0.52mM). See, for example, paragraph [7] of the present specification; Aerts et al. page 9, lines 1-21, page 14, line 31 through to page 15, line 17; and Priestman et al. (2000, Glycobiology 10:iii-ix; IDS Ref. BA). The Examiner's attention is again respectfully directed to page v, left column, third paragraph through to the right column, second full paragraph. It is noteworthy that the Priestman et al. reference was published in a peer reviewed journal and thus, was reviewed by independent scientists well versed in the art. That being the case, if the aforementioned prejudice had not existed, the corresponding assertions would have been deleted. In addition to its adverse effects with respect to glucocerebrosidase, it was also known to inhibit the activity of the ER enzyme α-glucosidase I in several cell types. See Platt et al. (1994, J. Biol. Chem. 269:8362-8365; IDS Ref. AP). It is, therefore, apparent that an ordinarily skilled artisan would have understood the prevailing opinion in the field and read

the Aerts et al. application within this context of knowledge.

With this in mind, Applicant respectfully asserts that the Examiner's interpretation of what is suggested in Tables 3, 4, and 5 of Aerts et al. appears to be influenced by hindsight reconstruction in light of results not available prior to the present invention. More particularly, the Examiner's statement that Aerts et al. demonstrate that agents such as NB-DNJ are sufficiently selective for glucosylceramidase over glucocerebrosidase that they can be used together stands in marked contrast to the teachings of the Aerts et al. application and general knowledge in the field. The data presented in the Tables must be read in light of the specification as a whole, which, as indicated above, recognizes that NB-DNJ is an inhibitor of glucocerebrosidase (IC_{50} = 0.52mM). To suggest that an ordinarily skilled practitioner would extrapolate from the data presented in Tables 3, 4, and 5 and arrive at the present invention, despite all of the teachings to the contrary in the Aerts et al. application and his/her general knowledge, is unreasonable.

In short, Aerts et al. do not teach a method for therapeutic intervention of Gaucher disease that calls for a combination of NB-DNJ and glucocerebrosidase. General knowledge at the time, in combination with the teaching of Aerts et al., would have led an ordinarily skilled practitioner to consider this combination to be inoperable and potentially deleterious to a patient with Gaucher disease due to the lack of specificity of NB-DNJ. Aerts et al. state this very clearly with respect to the non-lysosomal glucosylceramide synthase inhibitors available at the time, including NB-DNJ. See, for example, page 14 line 34 through to page 15, line 7. It is also noteworthy that Aerts et al. did not interpret the data presented in Tables 3, 4, and 5 to suggest that the specificity of NB-DNJ is sufficient enough to use in combination with glucocerebrosidase. That interpretation appears to be the invention of the Examiner. Aerts et al., as skilled practitioners, would certainly have offered such an assessment if this interpretation was evidenced by the data presented in these tables.

Moreover, Applicant asserts that the size of the genus that encompasses compounds and/or agents that are known to act as glucosylceramidase inhibitors is large and structurally diverse. Keeping in mind that both lysosomal glucocerebrosidase and non-lysosomal glucosylceramidase catalyze glucosylceramide hydrolysis, the genus of glucosylceramidase inhibitors includes agents that inhibit one or both of these enzymes. The genus, therefore, includes, for example: 1-phenyl-decanoylamino-3-morpholino-1-propanol (PDMP) and its

analogue 1-phenyl-2-hexadecanoylamino-3-morpholino-1-propanol (PPMP) [See, e.g., Aerts et al. page 8, lines 31-36 and reference cited therein]; butyl-deoxynojirimycin [See, e.g., Platt et al.; IDS Ref. AP]; butyl-deoxygalactonojirimycin [See, e.g., Platt et al.; IDS Ref. AR]; alkyl glucosides and derivatives thereof, wherein the number of carbon atoms on the alkyl chain varies; long chain alkyl galactosides (e.g., octyl β-D-galactoside); D-glucose; and glucosylsphingosine [See, e.g., Gopalan et al; IDS Ref. BB]; neutral or cationic acyl-beta-glucosides; alkyl beta-glucosides; octyl and dodecyl beta-glucosides; and lipids and N-hexyl derivatives [See, e.g., Gatt et al., IDS Ref. BC, Abstract only]; sphingosine; and conduritol B epoxide and its bromo (Br-) derivative [See, e.g., Grabowski et al Am Hum Gen 1985 IDS Ref. BD]; Br-conduritol B epoxide; deoxynojirimycin; castanospermine; glucosylsphingosine and its N-hexyl derivatives; and N-alkyl glucosylamines (with 10-18 carbons) [See, e.g., Grace et al. IDS Ref. BE]; N-hexyl-glucosylsphingosine [See, e.g., Warren et al.; IDS Ref. BF]; sulphated macromolecules (e.g., dextran sulphate and chondroitin sulphate) and non-ionic detergents [See, e.g., Shafit-Zagardo et al.; IDS Ref. BG, Abstract only]; cationic detergents; choline-containing and highly hydrophobic phospholipids [See, e.g., Blonder et al.; IDS Ref. BH, Abstract only]; castanospermine [See, e.g., Saul et al.; IDS Ref. BI, Abstract only]; and RNA, tRNA, and DNA nucleic acids [See, e.g., Sano et al.; IDS Ref. BJ]. In light of the size of the genus encompassed by the term "glucosylceramidase inhibitors" and the absolute absence of structural similarities among the species of this functional genus, Aerts et al. have failed to provide the necessary guidance on which basis an ordinarily skilled practitioner could even begin to assess which species among this genus could be used in combination with enzyme therapy. This defect underscores the fact that Aerts et al. is not an enabling reference for a combination therapy wherein any glucosylceramidase inhibitor is used in conjunction with enzyme replacement (e.g., glucocerebrosidase). The identification of a glucosylceramidase inhibitor that can be used in such a combination therapy would require undue experimentation on the part of an ordinarily skilled practitioner.

These arguments are corroborated by Dr. Morand's Declaration, which is submitted herewith along with his curriculum vitae, for the Examiner's consideration.

In view of the clarifying amendments to the claims and the above arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of the claims under 35 U.S.C. §102 and withdraw the rejection.

Rejections 35 USC § 112

Claims 1, 3, 14, 15, and 39-42 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for reciting that the agent capable of increasing the rate of glycolipid degradation is bone marrow transplantation. Although Applicant is not in complete agreement with the Examiner regarding this rejection, the claims are amended herein to expedite prosecution. More specifically, reference to bone marrow transplantation has been deleted from the claims. In light of the amendments to the claims, the rejection of claims 1, 3, 14, 15, and 39-42 under 35 U.S.C. §112, second paragraph is traversed.

In view of the above, the Examiner is respectfully requested to reconsider and withdraw the rejection of the instant claims under 35 U.S.C. §112.

Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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Attachments: Petition for a Three Month Extension of Time
Request for Continued Examination
Declaration by Dr. Morand
Exhibit A: Dr. Morand's Curriculum Vitae
Third Supplemental Information Disclosure Statement